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(54) Title: DRUGS AND USE THEREOF

(57) Abstract

The present invention relates to atenolol-based drugs intended for beta receptor blockade and for treatment of hypertension, and also a method for reducing, with the aid of these drugs, the toxic effect upon drug treatment in order to achieve the desired level of beta receptor blockade or the desired reduction in blood pressure upon drug treatment for hypertension.

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Drugs and use thereof

The present invention relates to beta-receptor-blocking drugs which are also effective against hypertension and whose active components include the previously known per se S-(-)-enantiomer of a previously known per se racemic beta-receptor-blocking substance with the generic name (trivial name) atenolol, i.e. (±)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide. According to the invention, replacement of atenolol by the S-(-)-enantiomer of atenolol in the drugs reduces their toxic effect.

Beta-receptor-blocking substances (hereinafter called beta blockers) are included in drugs which are used primarily for cardiovascular diseases, such as hypertension (high blood pressure), angina pectoris (vascular spasm) and certain arrhythmias, and on one ophthalmic disease (glaucoma). They exert their pharmacological effect by blocking the beta type of receptors for adrenergic substances, for example adrenaline and noradrenaline.

Some of the most commonly known side effects of treatment with beta blockers include reduced resting pulse rate, peripheral cold in the extremities, muscular weakness, tiredness, sleep disturbances, nightmares. In many cases

these, like the desired effect, are the consequence of the beta blockade. However, it has been suggested that in some cases other mechanisms are responsible for side effects, for example in the form of an effect on the central nervous system (CNS) or a decrease in the pumping power of the heart.

Most beta blockers, including atenolol, consist of substituted 3-aryloxy-2-hydroxypropylamines. A common feature of all these is that they have a chiral centre at carbon atom number 2. All substances containing a chiral centre may exist in two different isomeric forms, so-called enantiomers, which, fully in line with current practice, are referred to as the R-form and S- form respectively.

Hereinafter, as above, again fully in line with current practice, those substances consisting of equal parts of R-form and S-form are called racemic or racemate and those consisting principally of one of these two forms are called homochiral. The generic name (INN) atenolol relates by definition to the racemate.

It is already known that the pharmacological effects of chiral substances may to different extents be associated with their different enantiomers. This is explained by the fact that the human body, like nature as a whole, consists of an extremely complex chiral milieu in which the interaction between the endogenous substances, for example in the form of receptors and enzymes included therein, and the pharmacological substance supplied can take place in a number of different ways. A consequence of this is that the different enantiomers of one and the same chiral compound can give rise to both the same and completely different pharmacological effects, side effects, adverse reactions and toxic effects. However, it has not been possible, at least not as yet, to establish more general rules as to which enantiomer is most effective in each particular case or gives rise to the

greatest number of and most serious side effects.
It is likewise already known that the S-form of certain specific beta blockers belonging to the group of substituted 3-aryloxy-2-hydroxypropylamines exhibits practically all of the desired pharmacological effect of the corresponding racemate.

A small number of studies on the superiority of S-atenolol as a beta blocker compared to the R-form or the racemate have been published. Thus, for example, certain studies have been carried out on the affinity of the two enantiomers of atenolol to receptors in membrane from calf's lung and calf's heart, these studies showing that the S-form has a far greater affinity than the R-form. (Morris, T H, Kaumann, A J: Naunyn-Schmiedeberg's Arch Pharmacol 327, 176 (1984)).

In addition, it has been observed in tests carried out on rats that the S-form of atenolol has a hypotensive effect, while the R-form proved to be inactive. (Pearson, A A, Gaffney, T E, Walle, T, Privitera, P J: J. Pharmacol Exp Ther 250, 759 (1989)).

However, it is at present not known which side effects the R-form of atenolol has on animals or man but it is a well-known fact that the R-form of other beta blockers has a depressant effect on the heart. (Scriabine, A (Ed): Pharmacology of Antihypertensive Drugs, Page 317 (Kaplan, HR) Raven Press, NY (1980)).

The toxicity of beta blockers has generally been regarded as being a direct consequence of and therefore as being in proportion to their beta-blocking effects. Surprisingly, we have now been able to establish that a certain amount of atenolol (i.e. the racemate) exhibits the same toxicity as the same amount of its S-form in acute tests on rats, i.e. the R-form has been found to be as toxic as the S-form.

Therefore, we have now proposed that in future, instead of the racemate, the homochiral S-form of atenolol should be used for achieving an effect on the cardiovascular system, it being possible for the drug dosage to be reduced by about half. Such a change should mean that the toxic effects on the body are reduced by half.

The present invention thus concerns new drugs which contain homochiral S-atenolol as the pharmacologically active component, alone or in combination with other components, but which otherwise are made up of auxiliaries commonly used for drugs and are produced in a conventional manner. The invention also concerns the use of these drugs, only about half as much being employed as when the racemate is used.

The advantage of the present invention therefore lies in the fact that, in using a drug containing homochiral S-atenolol, only about half as great a dose needs to be used in order to obtain the same degree of beta blockade and/or blood pressure reduction as with a certain dose of racemic atenolol. In this way the toxic effects and the stress imposed on the body by the drug are reduced by about half, which is of great importance, since beta blockers are used in long-term therapy. The number of subjects taking 50-100 mg of racemic atenolol on a daily basis is probably of the order of magnitude of 10 million, in other words an extremely large number of people. Each one of these people consumes during their period of illness (if the latter is assumed to be about 20 years) approximately 1/4 kg of the R-form of atenolol, whose side effects have not been investigated but whose acute toxicity we have found, as mentioned, to be just as high as that of the S-form and which, regardless of side effects or toxicity, imposes a strain on the detoxifying functions of the body. It is therefore maintained that the present invention constitutes a significant possibility of improved treatment.

The invention is defined in the subsequent patent claims and is illustrated by the study described below and thus includes, as emerged from the above, on the one hand a drug and on the other hand a method for reducing the toxic burden on the human body in drug treatment with beta-receptor-blocking agents and in drug treatment of hypertension.

Toxicity study

A study was carried out on rats, in which the acute toxic effect of intravenously administered S-atenolol was compared with the corresponding effect of racemic atenolol.

Scope and plan of study

-10 CD rats per dose level and substance (racemate or S-form), - 5 dose levels.

- counting number of deaths.

Results of study

Within the 95 % confidence interval, the LD_{50} for S-atenolol was found to be 97-116 mg/kg, and for racemic atenolol 84-100 mg/kg, which means that in this test S-atenolol is as toxic as or possibly slightly less toxic than the racemate and thus, indirectly, also less toxic than the R-form.

PATENT CLAIMS

1. Drugs intended as beta-receptor-blocking agents and for treating hypertension, comprising 4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide as active component, characterised in that the said active component consists for the most part of S-(-)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide.

2. Drugs according to Claim 1, characterised in that the weight ratio between incorporated S-(-)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide and R-(+)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide is greater than 90:10.

3. Drugs according to Claim 1, characterised in that the said weight ratio is greater than 99:1.

4. Drugs according to Claim 1, characterised in that the only incorporated active component consists of 4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide, and in that they otherwise consist of auxiliary substances, which are conventional for medicines and drugs, and any impurities accepted in this context.

5. Method for reducing the toxic effect upon drug treatment with 4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetamide in order to obtain beta receptor blockade or as a drug for treating hypertension, characterised in that the active component used is S-(-)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide, and then only in about half as great an amount as when the racemate of the same compound (atenolol) is employed.

6. Method according to Claim 5, characterised in that the weight ratio between S-(-)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide and likewise incorporated

R-(+)-4-(2-hydroxy-3-isopropylaminopropoxy)phenyl-acetamide is kept greater than 90:10.

7. Method according to Claim 5, characterised in that the weight ratio between incorporated S-(-)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide and likewise incorporated R-(+)-4-(2-hydroxy-3-isopropylaminopropoxy)-phenylacetamide is kept greater than 99:1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00023

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/165, C 07 C 237/20

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US, A, 4085136 (HOWARD TUCKER) 18 April 1978, see particularly example 5 --	1-4
X	US, A, 4182911 (HOWARD TUCKER) 8 January 1980, see particularly example 5 --	1-4
X	EP, A1, 0193227 (GIST-BROCADES N.V.) 3 September 1986, see inter alia column 5 --	1-4
X	The Journal of Pharmacology and Experimental Therapeutics, Vol. 250, No. 3, May 1989 Amy Adams Pearson et al.: "A Stereoselective Central Hypotensive Action of Atenolol", see page 759 - page 763 --	1-4

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29th April 1991	1991 -05- 02
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Gunilla Claesson

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	Susan Budavari et al. "The Merck Index, eleventh edition", 1989, Merck & Co., Inc., USA, see page 136 no. 879, "Atenolol" --	4

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 5-7, because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods (PCT Rule 39.1 (iv)).

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00023

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-03-23
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4085136	78-04-18	CH-A-	611866	79-06-29
		DE-A-C-	2453324	75-05-22
		FR-A-B-	2250752	75-06-06
		GB-A-	1458392	76-12-15
		GB-A-	1458393	76-12-15
		JP-C-	1347813	86-11-13
		JP-A-	50077331	75-06-24
		JP-B-	61007412	86-03-06
		SE-B-C-	425971	82-11-29
		SE-A-	7414017	75-05-12
		US-A-	4182911	80-01-08
US-A- 4182911	80-01-08	CH-A-	611866	79-06-29
		DE-A-C-	2453324	75-05-22
		FR-A-B-	2250752	75-06-06
		GB-A-	1458392	76-12-15
		GB-A-	1458393	76-12-15
		JP-C-	1347813	86-11-13
		JP-A-	50077331	75-06-24
		JP-B-	61007412	86-03-06
		SE-B-C-	425971	82-11-29
		SE-A-	7414017	75-05-12
		US-A-	4085136	78-04-18
EP-A1- 0193227	86-09-03	AU-B-	589594	89-10-19
		AU-D-	5327086	87-04-30
		JP-A-	61257195	86-11-14